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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/918,585	07/30/2001	Avi J. Ashkenazi	P2630P1C1	3713

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EXAMINER	
TURNER, SHARON L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/918,585	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9, 11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet* .

Continuation of Attachment(s) 6). Other: AA902726 and AA689524 with associated public availability dates.

DETAILED ACTION

Priority

1. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e), 120 and 365(c) as follows:

If applicant desires priority under 35 U.S.C. 119(e) or 120 based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the

application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

This application is claiming the benefit of a prior filed nonprovisional application under 35 U.S.C. 120, 121, or 365(c). Copendency between the current application and the prior application is required.

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Applicant's have amended the first line of the specification as directed in the preliminary amendment submitted 7-30-01. The amendment identifies multiple US serial numbers, PCT international applications and provisional applications. However, the relationship of the multiple applications remains in question as the amendment fails to specifically point out the proper lineage and relationship amongst the members. Moreover, it is noted that not all members are co-pending and that multiple applications within the chain fail to support the content of SEQ ID NO:322, identified as PRO181. Applicant's have also submitted a supplemental communication providing a priority map which identifies particular applications in which PRO181 is disclosed. The map notes the first disclosure within US provisional 60/081,955 within Figure 2. However, there is no identified or apparent lineage that extends from the provisional to instant serial number. Applicant is required to clarify the priority claim in accordance with the above noted requirements including all co-pending applications and their designated

relationships upon which priority is claimed. As priority lineage cannot be definitively determined the application has been examined with the effective filing date of instant application filed 7-30-01.

*Due to the numerous number and incomplete disclosure of the relationships between the co-pending applications, the Examiner is unable to convey to applicant those priority documents required for foreign priority that have not been received.

Should the Applicant disagree with the Examiner's factual determination above, it is incumbent upon the Applicant to provide the serial number and specific page numbers of any parent application filed prior to 7-30-01 which specifically supports the claim limitations for each and every claim limitation in all the pending claims which Applicant considers to have been in possession of and fully enabled prior to 7-30-01.

Information Disclosure Statement

2. The Examiner notes corrections as to the public availability dates of Genbank Accession numbers AA902726 and AA689524 cited within the PTO-1449. Copies of the Accessions with the created public availability data are attached herein for Applicant's reference.

3. Utility is established based upon the chondrocyte redifferentiation assay noted for PRO 181, SEQ ID NO:322 at pp. 365 of the specification. The specification notes particular teachings with respect to PRO181, SEQ ID NO:322 at Figure 129, pp. 79-80, 174-75, 210, 277-278, 320, 326, 334, 351-352, and 364-365.

Specification

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

5. The specification is objected to because it contains an embedded hyperlink and/or other form of browser executable code. See p. 124, line 29.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 58-62 and 69-70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification describes a polypeptide sequence consisting of SEQ ID NO:322, which is shown to have activity in the chondrocyte redifferentiation assay and the glucose and/or FFA uptake assay as disclosed at pp. 351-352 and 364-365. However, the claims as written include polypeptides having at least 80-99% sequence identity with SEQ ID NO:322 but no particular biological activity or function. Thus, the claims are directed to a genus defined solely by homology comparison.

However, the instant disclosure of a single polypeptide, that of SEQ ID NO:322 with the instantly disclosed specific activities, does not adequately support the scope of

the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself."

Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus.

However, the instant specification discloses only the single sequence and no other members of the claimed genus. Given the unpredictability of homology comparisons, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000 and the fact that the specification fails to provide objective evidence of any additional sequences with the same requisite function, it cannot be established that a representative number of species have been disclosed to support the genus claim. No activity is set forth for the additional sequences and there is no evidence for a correlation or nexus provided between possession of any homologous feature and the activities of chondrocyte redifferentiation and/or glucose/ FFA uptake such that it is clearly conveyed that possession of any polypeptide having such structural similarity would possess the same function. Thus, the claims lack adequate written description support.

8. Claims 58-62 and 69-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:322 and peptides having 80% identity which exhibit activity in the chondrocyte redifferentiation assay, does not reasonably provide enablement for variable peptides with no requisite function as claimed. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

The skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000. For example, Jobling et al, Mol. Microbiol., 1991, 5(7):1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of conserved structural components to both biological function and immunological recognition.

Instant specification discloses a single PRO181 sequence that differs from the other sequences disclosed. The specification notes that the peptide is homologous to the cornichon family but fails to note such activity for the disclosed sequence. The specification teaches that the peptide tests positive in the chondrocyte redifferentiation assay and in the glucose and/or FFA uptake assay. Yet cornichon proteins are not disclosed as having such activities. The specification further fails to note such

conserved activities in any 80-99% variable molecule. In contrast, applicants claims are directed to peptides with 80-99% homology, to extracellular domains and to sequences lacking the associated signal peptide where no requisite function is required.

However, the specification does not enable this broad scope of the claims that encompasses a multitude of analogs or equivalents because the specification does not teach which residues can or should be modified such that the polypeptides retain sufficient structural similarity to evoke activity. The specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful and the skilled artisan would not necessarily expect functional conservation among homologous sequences. Moreover, no similar function is required of the additional sequences. The artisan would be unable to determine how to use such similar sequences that lack common function. The additional members would require further experimentation to discover their requisite use. Thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

Thus, in view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the

specification and the breadth of the claims the artisan cannot make and use the invention without undue experimentation.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 58-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 58-70 are directed to isolated peptides comprising "the extracellular domain" and "lacking its associated signal peptide". Page 122, lines 4-5 of the specification generally teaches that the PRO "extracellular domains" are a form of the PRO polypeptide "which is essentially free of the transmembrane and cytoplasmic domains." Figure 129 teaches that PRO181 possesses a "Type II transmembrane domain" at amino acids 11-31 and an "other transmembrane domain" at amino acids 57-77 and 123-143. The figure also teaches that the signal peptide is at amino acids 1-20. However, these limitations cannot be read into the claims and the specification fails to teach the orientation of the molecule with respect to the intracellular and/or extracellular portions. Further, the claim is directed to the extracellular domain lacking its associated signal peptides. However, signal peptides are not generally considered to be "associated with" extracellular domains and indeed in this particular incidence they do not appear to be adjacent (or associated) as identified. Moreover, the artisan does not readily recognize a signal sequence, intracellular, transmembrane or extracellular portions with respect to cornichon proteins, to which instant PRO181 is said to be homologus to, see also IDS reference Hillman et al., US Patent 5,968744, column 1,

lines 60-61, "There are no putative transmembrane or signal sequences (Roth, S et al., (1995), Cell 81:967-978). Thus, the metes and bounds of the recitations are indefinite with respect to those residues that are intended to be included or excluded by the claim recitations and the artisan is not provided definitive guidance whereby the residues may be determined. Accordingly, the metes and bounds of the residues included or excluded by the noted recitations is indefinite. Clarification of the particular amino acids is required.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 58-70 are rejected under 35 U.S.C. 102(b and e) as being anticipated by IDS reference Hillman et al., US Patent No. 5,968,744 issued Oct. 19, 1999.

Hillman et al., teach the human cornichon molecule (SEQ ID NO:1) which shares 100% sequence identity with instant PRO181, SEQ IDNO:322 identified as the peptide

encoded by the cDNA deposited in ATCC209775. The molecule thus comprises sequences having at least 80% homology to SEQ ID NO:322 and inherently comprises an extracellular domain as the peptides are the same. The peptide is produced recombinantly and includes constructs either with or without requisite signal sequences required for secretion. Hillman also teaches chimeric fusion constructs with various heterologous sequences including for example epitope tags such as His tags, factor XA, enterokinase or beta-galactosidase for purification, isolation or the production of particular antibodies, see in particular column 16, line 48-column 17, line 11, column 34, lines16-33 and column 20, line 54-column 21, line 5 and column 19, line 6-column 20, line 20. Thus, the reference teachings anticipate the claimed invention.

Status of Claims

13. No claims are allowed.

14. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
September 30, 2003